

## REMARKS

Claims 1-32 are pending. Claims 20-32 have been withdrawn from the Examiner's consideration. Claims 1-19 stand rejected. Claims 1, 5, 7, and 12 have been canceled, Claims 2-4, 6, 8-11, and 13-19 have been amended, and Claims 33-37 have been added. No new matter has been added. Reconsideration and allowance of Claims 2-4, 6, 8-11, 13-19, and 33-37 is respectfully requested.

### Information Disclosure Statement

The Examiner has requested an Information Disclosure Statement. An Information Disclosure Statement is submitted herewith. Applicants respectfully request consideration of the references in the Information Disclosure Statement.

### The Rejection of Claims 1-19 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1-19 under 35 U.S.C. § 112, first paragraph, for lack of an enabling written description. According to the Examiner, the invention requires the hydrophilic component of the composition to be a polyalkylene glycol or a polyalkylene oxide. Applicants respectfully disagree for the following reasons.

Claims 1, 5, 7, and 12, have been canceled. New independent Claim 33, from which Claims 2-4, 6, 8-11, 13-19, and new Claim 34 depend, is directed to a composition for enhancing transport through a cellular membrane comprising a hydrophilic conjugate comprising a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage. Claim 2 recites that the hydrophilic component is selected from a hydrophilic group, a hydrophilic polymer, and a hydrophilic therapeutic, diagnostic, or prophylactic agent. The specification clearly describes each of these three categories of hydrophilic components.

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A hydrophilic group is described as in the specification, for example, on page 22, lines 3-9. Representative hydrophilic groups are disclosed as including hydroxyacids, amines, thiols, molecules containing carboxyl groups, amino acids, and other small molecules.

The specification also provides a detailed description of hydrophilic polymers. Specification, page 20, line 30, to page 22, line 2. The specification clearly states that "a wide variety of hydrophilic polymers can be used to solubilize the hydrophobic polymer component before it is exposed to the stimuli at the site where delivery of the therapeutic, diagnostic or prophylactic agent is desired." Specification, page 20, line 30, to page 21, line 2. Moreover, although polyalkylene glycols and polyalkylene oxides are described as a preferred embodiment, other suitable hydrophilic polymers are also described, including polyethyleneoxide-polypropyleneoxide block co-polymers, polyvinyl-pyrrolidone, polyacrylamide or methacrylamide and their derivatives, polyacrylic or methacrylic acid, polyalkylacrylic acids, polyHema, polyvinyl alcohol, cellulotics, polysaccharides, and hydrophilic proteins or peptides. Specification, page 21, line 24, to page 22, line 2.

Hydrophilic therapeutic, diagnostic or prophylactic agent are described in the specification, for example, at page 22, lines 10-16. The specification clarifies that the hydrophilic therapeutic, diagnostic, or prophylactic agent has at least two effects: (1) it makes the hydrophobic polymer appear hydrophilic until after endocytosis, and (2) it has a therapeutic, diagnostic, or prophylactic effect. Specification, page 22, lines 10-16. A detailed description of therapeutic, diagnostic, and prophylactic agents is also provided in the specification, at page 24, line 30, to page 29, line 19. For example, "nucleosides, nucleotides or oligonucleotides, proteins or peptides, polysaccharides and other sugars, synthetic inorganic and organic compounds, metals or radioactive compounds or molecules" are disclosed as representative therapeutic and diagnostic agents. Specification, page 26, lines 6-9.

Therefore, the specification does not require the hydrophilic component to be a polyalkylene glycol or a polyalkylene oxide. Furthermore, the specification clearly provides an enabling written description of the three categories of hydrophilic components and, therefore, supports the scope of the hydrophilic components recited in Claim 1. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

The Rejection of Claims 1-19 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-19 under 35 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, the term "hydrophilic agent" in Claim 1 is vague and indefinite because it is unclear what type of effect this agent is producing. Claim 1 has been canceled, and none of the currently pending claims include the term "hydrophilic agent." Amended Claim 2 recites the term "hydrophilic therapeutic, diagnostic, or prophylactic agent", which is clearly defined in the Specification, as described above. Specification, page 22, lines 10-16. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

The Examiner also finds that the phrase "a therapeutic, diagnostic, or prophylactic agent" in Claim 2 is vague and indefinite because it is unclear how it is correlated with the hydrophilic component. Claim 2 has been amended to recite that the therapeutic, diagnostic, or prophylactic agent is an example of the hydrophilic component. This amendment is supported in the specification, for example, at page 22, lines 10-16. Applicants respectfully request withdrawal of this ground of rejection.

In addition, the Examiner states that Claims 1 and 2 contain improper Markush language. Claim 1 has been canceled. Claim 2 has been amended to correct the Markush language. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

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The Rejection of Claims 1-19 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-19 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,210,717 B1 (Choi et al.) and also as being obvious over U.S. Patent No. 5,939,453 (Heller et al.). According to the Examiner, Choi et al. discloses a composition comprising a copolymer transport molecule with a hydrophilic portion and a hydrophobic portion that can be joined by an amide or ester linkage. According to the Examiner, Heller et al. discloses a composition comprising block copolymers having both hydrophilic and bioerodable hydrophobic block joined by an ester linkage. The Examiner states that it would have been obvious to one skilled in the art to have the amide or ester linker in the polymers of Choi et al. and Heller et al. be cleaved as a function of pH. Applicants respectfully disagree.

To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the referenced teachings. In addition, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. M.P.E.P. § 706.02(j).

Claims 1, 5, 7, and 12, have been canceled. New independent Claim 20, from which Claims 2-4, 6, 8-11, 13-19, and new Claim 21 depend, is directed to a composition for enhancing transport through a cellular membrane comprising a hydrophilic conjugate comprising a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage, wherein the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component from the conjugate, and wherein the hydrophobic component is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate. Neither Choi et al. nor Heller et al. disclose or suggest a hydrophilic conjugate comprising a hydrophilic component and a hydrophobic

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component linked by a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH below 6.5. Nor do these references disclose or suggest a hydrophobic component in a hydrophilic conjugate that is membrane disruptive only when released from the conjugate to allow enhanced transport through a cellular membrane.

Moreover, the composition of Claims 9-11 further include a therapeutic, diagnostic, or prophylactic agent that is coupled to the hydrophilic or hydrophobic component in the conjugate by a degradable or disruptable linkage. Neither Choi et al. nor Heller et al. disclose an active agent that is coupled to a conjugate. Therefore, neither Choi et al. nor Heller et al. teach or suggest all the claim limitations. For this reason, the cited references fail to teach, remotely suggest, provide any motivation to make, or otherwise render obvious the claimed invention. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

#### New Claims 33-37

New independent Claim 33, from which Claims 2-4, 6, 8-11, 13-19, and new Claims 34-37 depend, is directed to a composition for enhancing transport through a cellular membrane comprising a hydrophilic conjugate comprising a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage, wherein the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component from the conjugate, and wherein the hydrophobic component is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate. Claim 34 recites that the composition further comprises a therapeutic, diagnostic, or prophylactic agent. Claim 35 recites that the hydrophobic component comprises a synthetic polymer. Claim 36 recites that the hydrophilic component comprises a polyalkylene oxide. Claim 37 recites that the pH-sensitive linkage comprises at least one of a acetal, orthoester, cisaconityl group, carboxylic acid hydrazone, phosphamide, ester, Schiff base, vinyl ether,

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dithioacetal, tert butyl ester, carbamate, urethane, anhydride, polysaccharide, amide, thiourea, urea, thioester, sulfonamide, phosphoramidate, or amine N-oxide. Support for Claims 33-37 can be found throughout the specification, for example, at page 5, line 20, to page 6, line 16; page 10, lines 5-22; page 10, line 23 to page 13, line 2; page 21, lines 1-4; page 22, line 20, to page 23, line 22; page 34, lines 1-9; page 38, lines 8-31. No new matter has been added.

Conclusion

In view of the foregoing amendments and remarks, applicants believe that Claims 2-4, 6, 8-11, 13-19, and 33-37 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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